

# Seroma Formation Following Axillary Dissection for Breast Cancer: Risk Factors and Lack of Influence of Bovine Thrombin

WILLIAM E. BURAK, JR., MD,<sup>1\*</sup> PATRICIA S. GOODMAN, RN, MS,<sup>1</sup> DONN C. YOUNG, PhD,<sup>2</sup>  
AND WILLIAM B. FARRAR, MD<sup>1</sup>

<sup>1</sup>*Department of Surgery, Division of Surgical Oncology, The Arthur G. James Cancer Hospital and Research Institute, Ohio State University College of Medicine, Columbus, Ohio*

<sup>2</sup>*Department of Biostatistics, The Arthur G. James Cancer Hospital and Research Institute, Ohio State University College of Medicine, Columbus, Ohio*

**Background:** Seromas of the axillary space following breast surgery can lead to significant morbidity and delay in the initiation of adjuvant therapy. A prospective, randomized study was undertaken to evaluate the effect of bovine spray thrombin on seroma formation following either modified radical mastectomy (MRM) or lumpectomy with axillary dissection (LAD). In addition, risk factors for seroma formation were analyzed and identified.

**Methods:** A total of 101 patients were randomized to receive either bovine thrombin (20,000 units) (treatment group) or no thrombin (control group) applied to their axilla following either MRM or LAD. Drains were left in place until the preceding 24-hour drainage was <40 milliliters. The number of days the drains were in place and wound complications (including seroma formation) were recorded.

**Results:** Forty-nine (n = 49) patients were assigned to the treatment group and 52 (n = 52) to the control group. MRM was performed on 60 patients (59%) and LAD on 41 (41%). Eighteen of the 49 patients (37%) in the thrombin group developed a seroma in comparison to 21 of the 52 control patients (40%) ( $P = 0.71$ ). Significant risk factors for seroma formation included increased age, patient weight, initial 72-hour wound drainage, and LAD. No statistically significant differences were observed between treatment and control groups with respect to time to drain removal, or the incidence of other wound complications.

**Conclusion:** Although thrombin by itself appears to have no effect on subsequent seroma development following axillary dissection, the identification of predictive variables will be helpful in designing future trials aimed at reducing the incidence of this common complication of breast surgery. *J. Surg. Oncol.* 64:27–31 © 1997 Wiley-Liss, Inc.

**KEY WORDS:** breast cancer; axilla; seroma; thrombin

## INTRODUCTION

One of the most frequent complications encountered in breast surgery is the development of an axillary seroma. The rate of this occurrence ranges from 18% to 59% following operations for breast carcinoma [1–5]. Viewed as more of a nuisance than a serious complication, seromas may become infected, cause flap necrosis, and in-

crease the likelihood of lymphedema of the arm [6,7]. Additionally, a delay in wound healing may necessitate postponement of subsequent adjuvant therapy. Although closed suction drains of the axillary space have been

\*Correspondence to: William E. Burak, Jr., M.D., Department of Surgery, Division of Surgical Oncology, N914 Doan Hall, 410 W. 10th Avenue, Columbus, OH 43210.

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shown to decrease the likelihood of seroma formation, these troublesome fluid collections continue to contribute to the morbidity of both modified radical mastectomy and lumpectomy with axillary dissection [8,9]. If this complication could be further minimized, patients would benefit from a reduction in superfluous postoperative visits and anxiety over treatment delays, and the incidence of infection and other difficulties in wound healing would be lessened.

Traditionally, it is thought that seroma formation occurs as a consequence of both lymphatic disruption and oozing of capillary beds following axillary node dissection. Interference with this response should decrease the amount of wound drainage and thus minimize the formation of seromas. Furthermore, any technique that could potentially obliterate the "dead space" associated with axillary dissection also might lessen the incidence of this complication. Bovine thrombin clearly has been demonstrated to be an effective hemostatic agent while possessing the ability to form a "fibrin seal" when combined with fibrinogen. These two mechanisms of action could be of great benefit in seroma prevention.

Although brief reports have described the use of thrombin in head and neck surgery, its use in breast surgery has not been reported in a prospective trial [10]. A prospective, randomized study was therefore designed and conducted to examine the effects of topical spray thrombin on wound drainage and fluid collections following surgery for breast cancer. In addition, this trial attempted to identify patient characteristics that increase the risk of developing a postoperative seroma.

## MATERIALS AND METHODS

From November 1989 to July 1992, women with known carcinoma of the breast who were to undergo either modified radical mastectomy (MRM) or lumpectomy with axillary dissection (LAD) were enrolled in this study. After obtaining informed consent (approved by the Institutional Review Board at Ohio State University), patients were randomized into either the treatment or control group. Lumpectomy with axillary dissection or modified radical mastectomy was then performed on all patients. Both procedures included dissection of levels 1, 2, and 3 axillary lymph nodes as well as resection of the pectoralis minor muscle. Prior to closure, the treatment group had 20,000 units (20 mls) of bovine thrombin (Thrombostat®, Parke-Davis, Morris Plains, NJ) sprayed to the axillary chest wall and interior of the skin flaps followed by 5-minute waiting period. Both groups had sutures placed to "tack" the skin flaps to the chest wall, as described previously [11]. The wound was then closed over two closed suction drains, one in the axilla (all patients) and the other under the skin flaps (mastectomy patients only), and a dressing applied for 48 hours. All operations were supervised or performed by the same

attending surgeon. Full range of motion exercises were delayed until the drainage systems were removed. Patients were discharged home with their drains, where they recorded daily outputs. Follow-up was done in the outpatient clinic where drainage systems were pulled when their output was <40 mls per 24-hour period, or when the drain was no longer functional.

Axillary seromas were defined as any clinically apparent fluid collection in the axilla and were treated with multiple aspirations or in persistent cases, new drain insertion. All patients in which there was clinically a suspicion of a seroma underwent an attempt at aspiration.

Variables recorded included patient weight, age, obesity index (Quetelet index), and breast weight (when available). Also collected was the total number of lymph nodes removed and the total number of positive nodes per patient. Wound drainage was documented, as was the duration the drains were left in place. Wound complications were noted and classified as cellulitis, abscess, flap necrosis, dehiscence, or seroma.

## Statistics

Comparisons of patient groups for continuous data were performed using analysis of variance. Nominal data were analyzed using Chi-square tests or, when sample sizes were very small, Fisher's exact test. Evaluation of risk factors related to seroma formation used stepwise logistic regression. Values are stated as means  $\pm$  standard deviation.

## RESULTS

All 101 patients who were enrolled completed the trial. Forty-nine ( $n = 49$ ) patients were assigned to the treatment group and 52 ( $n = 52$ ) to the control group. Modified radical mastectomy was performed on 60 patients (59%) and lumpectomy with axillary dissection on 41 (41%). Mean age was  $54.6 \pm 13.6$  (range 31–86) years, patient weight was  $68.9 \pm 14.2$  (range 40–140) kg, obesity index  $26.5 \pm 5.7$  (range 17–54). The mean breast weight in the modified radical mastectomy patients was available in 44 patients and was  $841.7 \pm 412.9$  (range 220–2115) g. The total number of nodes removed and the number of positive nodes were  $22.4 \pm 9.4$  (range 7–68) and  $2.5 \pm 6.6$  (range 0–53), respectively. The mean postoperative time until drain removal was  $10.2 \pm 5$  (range 4–30) days and the amount of drainage in the first 72 hours after surgery was  $447.3 \pm 200$  (range 123–1100) ml. A comparison of the treatment and control group patient characteristics is shown in Table I.

Wound complications were seen in 47 patients and are listed in Table II. An axillary seroma developed in 39 patients (38.6%). Eighteen of the 49 patients (37%) in the

**TABLE I. Characteristics of Study Patients Treated With Thrombin (n = 49) Compared to Controls (n = 51)**

	Thrombin	Control	<i>P</i> value
Age (years) <sup>a</sup>	53.5	55.7	0.424
Operation			0.719
lumpectomy/axillary dissection	19	22	
modified radical mastectomy	30	30	
Weight (kg) <sup>a</sup>	70.5	67.3	0.270
Obesity index <sup>a,b</sup>	27.3	25.6	0.122
Breast weight (kg) <sup>a</sup> (n = 44)	978.1	692.3	0.020
# total nodes <sup>a</sup>	22.6	22.2	0.816
# positive nodes <sup>a</sup>	2.0	3.1	0.400

<sup>a</sup>Mean value.<sup>b</sup>Obesity index = patient weight (kg)/height(m)<sup>2</sup>.**TABLE II. Patients Treated With Thrombin (n = 49)\***

	Thrombin	Control	<i>P</i> value
Seroma (# patients)	18	21	0.710
Other wound complication (# patients) <sup>a</sup>	3	5	0.516
72° wound drainage (mls)	439	455	0.690
Day of drain removal	10.3	10.0	0.730

\*There were no significant reduction in seromas, wound complications, drainage, or length of drainage when compared to controls (n = 51).

<sup>a</sup>Other wound complications included minor wound dehiscence (5 patients), abscess (3 patients).

thrombin group developed a seroma in comparison to 21 of the 52 control patients (40%) ( $P = 0.71$ ). No significant differences were observed in rates of other wound complications.

When the results of the initial 72-hour wound drainage were compared, no significant differences were seen as a result of treatment with thrombin; the treatment group drained an average of  $439 \pm 197$  ml vs.  $455 \pm 205$  ml in the control group ( $P = 0.69$ ). The mean day of drain removal was  $10.3 \pm 5.5$  for the patients in the thrombin group and  $10.0 \pm 4.6$  in controls ( $P = 0.73$ ).

The impact of several patient variables on seroma formation were analyzed in order to determine their predictive value. Univariate analysis identified several factors associated with seroma formation (seen in Table III). Although it appears that delayed drain removal predisposed patients to seroma formation, this is likely due to the increased amount of drainage in these patients, which is also a predisposing factor. Using logistic regression, the amount of wound drainage in the first 72 hours, the type of operation performed (LAD vs. MRM), increasing patient age, and increasing patient weight were found to be highly predictive of subsequent seroma formation (Table IV). Although these variables were statistically significant, no cutoffs for the values were identified. The *preoperative* variables found to be significant included

LAD ( $P < 0.001$ ), increased age ( $P = 0.016$ ), and increased patient weight ( $P = 0.044$ ).

## DISCUSSION

Surgery of the axillary space is associated with numerous complications, including infection, hematoma, flap necrosis, lymphedema of the ipsilateral upper extremity, and postoperative fluid collections (seromas). Multiple studies have been performed aimed at preventing seromas, some with encouraging results. Arm immobilization, closed suction drainage, and flap tacking sutures all have been shown to decrease this incidence; however, it remains a significant complication [5,9,11,12]. The exact etiology of seroma formation remains controversial. Some cite the surgical disruption of lymphatics and capillaries, coupled with creation of dead space [3,4,11]; others maintain that postmastectomy fluid collections are not true "seromas" or lymphatic collections, but are actually inflammatory exudates that accumulate in this dead space [13].

Bovine thrombin has recently enjoyed attention in the surgical literature due to its effectiveness as a hemostatic agent, enjoying widespread use in vascular and cardiothoracic surgery. Combined with human fibrinogen, in the form of cryoprecipitate, bovine thrombin has the additional capability of creating "fibrin glue," which also has many clinical applications [14–16]. Lindsey et al. [10] demonstrated a clear reduction in the rate of seroma formation with the use of fibrin glue in a rat model following modified radical neck dissection. In a similar animal study, fibrin glue was shown markedly to reduce the incidence of fluid collections in rats after modified radical mastectomy [17]. Two small retrospective reports from Europe have looked with mixed results, at the application of fibrin glue in humans following axillary dissection [18,19].

A serious drawback to the routine use of fibrin glue lies in the possibility of disease transmission through cryoprecipitate, a pooled blood product. When used by itself, thrombin may demonstrate hemostatic properties when combined with autologous fibrinogen, which will form fibrin. The present study is the first report using topical thrombin in patients undergoing surgery for breast cancer. In designing the trial, the hypothesis was that the hemostatic properties of thrombin would aid in preventing postoperative capillary leakage, decrease wound drainage, and subsequent seroma formation.

The results fail to show a significant decrease in the amount of wound drainage or seroma formation in the patients treated with thrombin. This suggests that thrombin's hemostatic properties are inadequate to decrease wound drainage, and this agent may need to be combined with fibrinogen to provide a more effective "sealant" and obliterate dead space. With the increased application of viral inactivation techniques, safe purified human

**TABLE III. Characteristics of Patients Forming Seromas (n = 39) Compared to Patients not Forming Seromas (n = 62) to Identify Predictive Variables for Seroma Formation (using univariate analysis)**

Variable	Seroma	No seroma	<i>P</i> value
72° wound drainage (mls) <sup>a</sup>	569.2 ± 221.1	374.1 ± 145.2	<0.001
Day drain removed <sup>a</sup>	12.5 ± 5.9	8.7 ± 3.7	<0.001
Patient weight (kg) <sup>a</sup>	74.9 ± 16.6	65.0 ± 10.9	<0.001
Obesity index <sup>a</sup>	28.6 ± 6.5	25.1 ± 4.6	0.002
Operation performed (# patients)			0.010
lumpectomy/axillary dissection	22	19	
modified radical mastectomy	17	43	
Age (yr) <sup>a</sup>	58.5 ± 13.1	52.2 ± 13.5	0.023
Breast weight (kg) <sup>a</sup>	1013 ± 514.3	769.6 ± 346.9	0.073
# total nodes <sup>a</sup>	21.9 ± 9.3	22.7 ± 9.5	0.068
# positive nodes <sup>a</sup>	3.7 ± 9.6	1.8 ± 3.6	0.890

<sup>a</sup>Values given as mean ± standard deviation.**TABLE IV. Characteristics of Patients Forming Seromas (n = 39) Compared to Patients not Forming Seromas (n = 62) to Identify Predictive Variables for Seroma Formation (using multivariate analysis)**

Variable	<i>P</i> value
Lumpectomy/axillary dissection	<0.001
72° wound drainage	0.001
Age	0.016
Patient weight	0.044
# total nodes	0.268
Day drain removed	0.820
Obesity index	0.823

thrombin and fibrinogen will be available for clinical use, which may resolve this shortcoming [20].

Predictive variables for seroma formation were found to include the amount of wound drainage in the first 3 postoperative days, lumpectomy/axillary dissection (vs. modified radical mastectomy), age, and patient weight. This is consistent with the findings of previous authors who identified age and quantity of wound drainage, respectively, as risk factors [1,3]. This observation is most likely explained by both less efficient wound healing in older participants and a larger axillary “dead space” created in heavier patients. It is unclear why lumpectomy/axillary dissection is associated with seroma formation in the present study. Possible explanations include more effective drainage in mastectomy patients (2 drains vs. 1 drain), or less adequate exposure during lumpectomy/axillary dissection resulting in more tissue trauma (and subsequent drainage) during dissection. Furthermore, the increased seroma formation in LAD patients may be due to the continued presence of the breast and its contribution to lymphatic flow. The high rates of seroma formation in this study are most likely related to the levels 1, 2, and 3 axillary dissection (with resection of pectoralis minor) performed during the study period. A levels 1 and 2, dissection is now routinely performed at

our institution. Nevertheless, it appears that a “high risk group” can be identified preoperatively and techniques aimed at seroma reduction implemented.

## CONCLUSION

A total of 101 consecutive patients were studied in a randomized, prospective trial to evaluate the effect of bovine thrombin applied to axillary wounds following surgery for breast cancer. The trial failed to show a significant reduction in the incidence of seromas. However, several risk factors for seroma formation were identified using multivariate analysis, including patient weight, type of operation (lumpectomy/axillary dissection), and age. Future trials will examine combining human thrombin with concentrated fibrinogen in a effort to produce a stronger, more effective sealant.

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